REMARKS

Upon entry of this amendment, claims 1-9 and 32-51 will be pending. Claims 10-31 are canceled.

Claims 1, 48, and 49 have been amended. Support for the amendments to claims 1, 48, and 49 may be found, for example, in the specification as filed at page 14, lines 9-11.

With this amendment, no new matter has been added.

I. 35 U.S.C. 103(a)

Reconsideration is requested of the rejection of claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49-51 under 35 U.S.C. 103(a) as being unpatentable over Gough et al.[1], in view of Kodadek[2] and Petrenko et al.[3]

Claim 1 is directed to a method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus and ***an antifungal activity*** comprising (a) constructing a library of peptides by, (i) preparing random oligonucleotides; (ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell; (iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector; (b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector; (c) eluting bound vector from said fungus; (d) amplifying said bound vector; (e) sequencing the oligonucleotides contained in said eluted vector; (f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and (g) selecting the non-immunoglobulin peptides ***having antifungal activity*** and for which the amino acid sequence has been deduced.

Claim 49 is directed to a method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus and ***an antifungal activity*** comprising (a) constructing a library of peptides by, (i) preparing random oligonucleotides; (ii) inserting said oligonucleotides into a vector that expresses

[1] Gough et al., *J. Immunol. Methods*, 228: 97-108 (1999).
[2] Kodadek, U.S. Patent Application Publication No. 2001/0029024.
[3] Petrenko et al., *Protein Engineering*, 9(9): 797-801 (1996).

peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell; (iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector; wherein the library of peptides is (1) an f8-1 peptide library, wherein each peptide of the f8-1 peptide library has a length of 8 amino acids or (2) an f88-4 peptide library, wherein each peptide of the f88-4 peptide library has a length of 15 amino acids; (b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector; (c) eluting bound vector from said fungus; (d) amplifying said bound vector; (e) sequencing the oligonucleotides contained in said eluted vector; (f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and (g) selecting the non-immunoglobulin peptides ***having antifungal activity*** and for which the amino acid sequence has been deduced.

The Office indicated that "[i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute a [sic] small molecular weight compounds as peptides in the method of Gough as taught by Kodadek and Petrenko."[4]

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some reason for having made the combination. If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then one skilled in the art would not have had a reason to have made the proposed modification.[5]

A. Gough et al.

Gough et al. describe methods for the isolation of ***antibodies*** specific for surface-exposed epitopes on certain species of *Phytophthora* to be used for production of immunological probes and single-chain Fv (scFv) antibodies.[6] Gough et al.'s method involves adding germlings and soluble components thereof to maxisorb immunotubes, blocking, and incubating the maxisorb immunotubes with a ***phage-displayed antibody***

[4] Examiner's Answer to Appeal Brief, June 1, 2008, page 4.
[5] MPEP § 2143.01.
[6] Gough et al. at page 98.

library.[7] The nonbound phage is removed, and the bound phage eluted and amplified in *E. coli*.[8] These steps are repeated, resulting in a discrete population of phage antibody fragments.[9] The diversity of the eluted antibodies is established by *Bst*NI fingerprinting, and DNA encoding for selected single-chain Fv antibodies is amplified by PCR, digested with restriction endonucleases, and ligated into a vector to produce scFv fusion proteins.[10] The scFv fusion proteins are then used to recognize external epitopes of *Phytophthora*.[11]

While the methods of Gough et al. were generally effective in identifying antibodies that bind to the surface of *Phytophthora*, Gough et al. admit that their antibodies and others identified to date **have had no effect on *Phytophthora* whatsoever**. Gough et al. still promise, however, that other antibodies to surface epitopes of *Phytophthora* having a pathogenic effect could still be identified:

> The panning of whole pathogens might be expected to yield scFvs that bind to unmodified surface antigens that may be of importance in the infection process. However, preliminary assays, in which sporangia were mixed with soluble MBP-scFv fusion protein and then used to inoculate tomato leaf discs (Niderman et al., 1995), showed no detectable anti-fungal activity for any of the antibodies. Nevertheless, the isolation of other scFvs specifically directed against the native conformation of surface-accessible antigens may well provide new tools to probe and manipulate pathogenicity.[12]

In contrast to the methods of Gough et al., claims 1 and 49 require the use of a library of non-immunoglobulin peptides, not a library of scFv antibody fragments. Because Gough et al. are concerned with the isolation of ***antibodies*** for the surface-exposed epitopes on certain *Phytophthora* species to be used for ***immunological*** probes, they are using only single-chain Fv antibody fragments on phage in their disclosed phage display methods, and report no problems with the use of such antibody fragments for their objectives. Significantly, therefore, not only do Gough et al. fail to

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[7] *Id*. at page 99.
[8] *Id*.; *see also* pages 101-102.
[9] *Id*.
[10] Gough et al. at pages 98-99; *see also* pages 102-103.
[11] *Id*. at page 100; *see also* pages 103-104.
[12] *Id*. at 107.

provide a reason for the use of vector-displayed random ***peptide*** libraries in their methods, they also fail to provide a reason for the selection of ***non-immunoglobulin*** peptides that bind epitopes on the surface of a fungus.[13] Furthermore, the substitution of random peptide libraries for antibody fragment libraries would be unproductive as Gough et al. seek to identify antibodies which can be used in immunological methods, not mere non-immunoglobulin peptides.[14]

A person of skill in the art must ignore the express teachings of Gough et al. to arrive at a non-immunoglobulin approach using simple peptide libraries. Most significantly, Gough et al.'s approach did not work, i.e., it "showed ***no detectable anti-fungal activity for any of the antibodies***," and, at best, they hold out some vague hope for the future but this hope was limited to scFvs and ***not*** non-immunoglobulin peptides. Thus, a person of skill in the art would have had no reason to substitute a library of peptides for antibodies in the methods of Gough et al. for the selection of non-immunoglobulin peptides.

The Office vaguely asserts that "the suggested teachings of Gough of non-macromolecular species (i.e., fragments) that retain the recognition characteristics of antibodies like small molecule peptides mimics [*sic*], would suggest the claimed peptide."[15] In fact, Gough et al. teaches and emphasizes the use of antibodies and only antibodies, not simply "species that retain the recognition characteristics of antibodies" as asserted by the Office. In sharp contrast, the Applicants' invention functions independently of immunological response (i.e., non-immunoglobulin) and is claimed as such.[16] Just because you happen to have a peptide that binds to an epitope does not mean that it is an "antibody mimic," as the Office is apparently asserting.

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[13] *See* application as filed, page 9, lines 16-19 ("A "non-immunoglobulin peptide" means a peptide which is not an immunoglobulin, a recognized region of an immunoglobulin, or contains a region of an immunoglobulin. For example, a single chain variable region of an immunoglobulin would be excluded from this definition.").
[14] *In re Gordon*, 733 F.2d 900, 221 USPQ2d 1125 (Fed. Cir. 1984); M.P.E.P. §2143.01. As stated by the Federal Circuit, if proposed a modification would render the prior art unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.
[15] Office action dated July 25, 2005, at page 3.
[16] *See* claim 1 *and* application as filed, page 9, lines 16-19.

B. Kodadek

Kodadek describes methods of isolating small peptides that recognize **specific, known target peptides** (i.e., target peptides the identity and sequence of which are already known) for use in affinity purification. Kodadek's methods involve an elaborate genetic selection scheme to identify certain library encoded peptides having affinity to a single known target peptide (i.e., not a multitude of ***unknown*** epitopes such as those on the surface of a fungus).

Briefly, Kodadek's genetic selection scheme involves forming two compatible constructs, one encoding the known target peptide, and the other encoding a library of DNA fragments, and transforming them into *E. coli*.[17] If a library encoded peptide is present in the library that associates with the target peptide, a complex between the library encoded peptide and the target peptide is formed.[18] The complex blocks certain operator regions in *E. coli*, making it resistant to phage infection challenge.[19] Resistant colonies may then be selected, and the library encoded peptides that bind to the target peptide isolated.[20] As one example, Kodadek discloses utilizing as the target peptide a 13-residue sequence from the protease cleavage site of the human insulin-like growth factor I (IGF-I).[21]

In contrast to the Applicants' claimed invention, Kodadek is concerned with the selection of library encoded peptides having affinity to a ***single, specific, known target peptide***, not a surface with a multitude of unknown epitopes such as the surface of a fungus. Kodadek is not contacting his library encoded peptides with anything other than a provided target peptide (e.g., the protease cleavage site of the human insulin-like growth factor I) to identify binding partners to that particular target.

Furthermore, Kodadek actually **teaches away** from the use of phage display methods to identify library encoded peptides. Specifically, Kodadek suggests the superiority of his elaborate genetic selection scheme, where other methods have failed. In so doing, Kodadek notes that both **random peptides** (used in the present invention) and antibodies (used in Gough et al.) are **inadequate** for his purpose. As such,

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[17] Kodadek, page 4, paragraph [0042].
[18] *Id.*; *see also* Kodadek, Figure 1.
[19] *Id.*
[20] *Id.*
[21] *Id.* at page 4, paragraph [0039].

Kodadek and Gough et al. represent mutually exclusive domains, and, therefore, any suggestion of substitution of the peptides of Kodadek into the methods of Gough et al. would not be feasible. Thus, one skilled in the art would not and could not be motivated to substitute the highly specialized method of Kodadek into the method of Gough et al. without violating the objective of Gough et al. and rendering it unsatisfactory for its intended purpose.[22]

Instead of providing a reason to combine the references, a close reading of Kodadek clearly indicates that one skilled in the art would actually be ***guided away*** from combining the disclosures of Gough et al. and Kodadek. Kodadek describes his genetic selection scheme designed to be an improved method, in and of itself, to overcome past failures in identifying peptide complexes. It is only after particular, weakly-binding library encoded peptides that bind to the known target peptide are identified by the genetic selection scheme (i.e., on the basis of affinity) that Kodadek coupled them with conventional phage display methods to form a pincer. Thus Kodadek clearly implies (and in some respects states outright) that conventional phage display methods, standing on their own, would not work. Why else would Kodadek go to all the trouble of devising the genetic selection scheme if random peptide phage display alone would be effective?

C. Petrenko et al.

Petrenko et al. describe methods of forming phage-displayed "landscape libraries" having complex surface functions that would be useful, e.g., in nanotechnology applications. According to Petrenko et al., the complex surface functions of phage clones depend on interactions between neighboring groups of display peptides and wild-type peptides.[23] The emergent properties of the phage surface inhere (i.e., are intrinsic) in the ***entire surface of the phage***, not in the display peptides themselves.[24] Stated another way, Petrenko et al. describe modifications to phage such that the phage will display "global properties" across the entire surface of the phage, not only mere localized properties of the particular displayed peptides. As an example, Petrenko

[22] *See supra*, note 37.
[23] Petrenko et al. at page 797.
[24] *Id.*

et al. suggest as desirable a phage with a high affinity for a metal ion that displays metal complexed on the surface in a specific repeating geometry.[25] Petrenko et al. also specifically disclose experiments where phage clones were selected for the "global property" of chloroform resistance.[26] Petrenko et al. also describe panning phage displayed peptides against a particular known target material. Such targets included dioxin in one experiment and the lectin concanavalin A in another experiment. In both cases, the phage displayed library of peptides was panned against a **single known target** (i.e., not a multitude of unknown targets such as those on the surface of a fungus).

In contrast to the focus and methods of Petrenko et al., claims 1 and 49 are directed to the identification of peptides displayed on the surface of a vector that have antifungal activity and a binding affinity for epitopes displayed on the surface of *Phytophthora*. This goal does ***not*** necessarily implicate "global functions" that inhere in the entire surface of phage-peptide. In fact, claims 1 and 49 do not even require that the peptide library be expressed on phage. Rather, the peptide library is expressed on a vector, and any vector capable of expressing the peptides of the peptide library may be used.[27] Contrary to the Office's assertion otherwise, the mosaic nature of phage-displayed peptides in Petrenko et al. provides no reasons to substitute peptides for antibody fragments in the method of Gough et al. in order to identify non-immunoglobulin peptides with antifungal activity and an affinity for surface epitopes of *Phytophthora*.

Finally, the Office asserts that Petrenko et al. extol the "global functions" that inhere in the entire surface landscape of phage-peptide as motivation to substitute peptides for antibody fragments in the method of Gough et al. As stated above, however, the objectives of Petrenko et al. (global functions) and Gough et al. (antibodies) are far too disparate for one skilled in the art to make such a substitution, particularly since such a substitution would render the prior art being modified unsatisfactory for its intended purpose.[28]

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[25] *Id.* at 801.
[26] *Id.* at 789-799.
[27] *See* application as filed, page 11, lines 3-19.
[28] *See supra,* note 37.

D. The prior art provides no reasonable expectation of success

Collectively, and individually, Gough et al., Kodadek and Petrenko et al. fail to disclose a method for the identification of a peptide, immunoglobulin or otherwise, having anti-fungal properties. Gough et al. merely identified immunoglobulin peptides that bind to the surface of *Phytophthora*; ***Gough et al. failed to demonstrate that their scFvs had any antifungal effect*** and merely expressed some vague hope that **scFvs** may ***one day*** "provide new tools to probe and manipulate pathogenicity."[29] ***Kodadek was not concerned with the identification of peptides having antifungal properties.*** Instead, Kodadek was concerned with two-hybrid methods and modifications thereto for isolating small peptides that recognize specific, known target peptides for use in affinity purification; significantly, however, Kodadek developed this approach because ***the random peptide approach*** (used in the present invention) and antibodies (used in Gough et al.) ***were inadequate*** for his purpose. Petrenko et al. were concerned with forming phage-displayed "landscape libraries" of general applicability and ***did not suggest any means for identifying antifungal peptides***.

Against this backdrop, claims 1 and 49 define methods which have been successfully used to identify non-immunoglobulin peptides ***which have been demonstrated to yield peptides having antifungal properties***. According to the Office, this approach was obvious despite the fact that Gough et al., the only reference cited by the Office relating to antifungal peptides, ***failed to identify any peptides having antifungal properties*** and Kodadek said the random peptide approach ***failed completely***.[30] Somehow, the Office has concluded a person of ordinary skill would have been led to adopt the method of claims 1 or 49 with an expectation of success despite the fact that not one of the three references cited by the Office successfully accomplished this and one of them said that prior attempts to use Applicants' approach failed completely.[31] Simply stated, the Office's rejection of claims 1 and 49 is nothing

[29] Gough et al. at page 107.
[30] Kodadek, page 4, paragraph [0038].
[31] *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-8, 18 USPQ2d 1016, 1022-23 (Fed. Cir. 1991) *cert. denied*, 502 U.S. 856 (1991).

more and nothing less than an impermissible hindsight rejection, using Applicants' disclosure as a template.[32]

Claims 2-4, 6-9, 32-34, 37-43, 45-47, 50, and 51, which depend from at least claim 1 and/or claim 49, are patentable over Gough et al. in view of Kodadek and Petrenko et al. for the reasons stated with respect to claims 1 and 49 and by reason of the additional requirements each claim introduces.

II. Claims 5, 35, 36, 44, and 48

Claims 5, 35, 36, 44, and 48 are listed as rejected on page 1 of the Office action; however the rejection of the same, for either new or prior stated reasons, is not clearly indicated in the body of the Office action, as there are no recited grounds for rejection.

According to 37 C.F.R. 1.113, in a final Office action, the Office shall repeat each applicable ground of rejection:

> (a) On the second or any subsequent examination or consideration by the examiner the rejection or other action may be made final, ...
>
> (b) In making such final rejection, *the examiner* ***shall repeat or state all grounds of rejection then considered applicable*** *to the claims of the application, clearly stating the reasons in support thereof.*[33]

The mandatory nature of this requirement is reflected in the Manual of Patent Examining Procedure (M.P.E.P.):

> **STATEMENT OF GROUNDS**
>
> In making the final rejection, *all outstanding grounds of rejection of record should be carefully reviewed,* ***and any such grounds relied on in the final rejection should be reiterated***.[34]

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[32] M.P.E.P. §2141; *U.S. v. Adams, 383 U.S. 39 (1965); Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985), *vacated and remanded on other grounds*, 475 U.S. 809, 106 S.Ct. 1578 (1986), *adhered to on remand*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir. 1987); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

[33] 37 C.F.R. 1.113(a) and (b) (emphasis added).

[34] M.P.E.P. § 706.07 (emphasis added).

Thus, Applicants understand the rejection of these claims as stated on page one of the Office action to be incorrect and assert that these claims are allowable. Accordingly, Applicants request clarification of the status of these claims in the next Office communication.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-4, 6-9, 32-34, 37-43, 45-47, and 49-51 under 35 U.S.C. 103(a), and allowance of all claims as presented herein.

The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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